Rheumatoid Arthritis and Accelerated Atherogenesis

To the Editor:

In their outstanding review, Sattar et al. discussed the association between rheumatoid arthritis (RA) and accelerated atherogenesis mediated by systemic inflammatory response. We have recently described severe subclinical atherosclerotic findings in long-term actively treated RA patients (n=47) without clinically evident atherosclerosis or its complications.2

Sattar et al.1 underlined the importance of endothelial dysfunction as an initial step in the development of atherogenesis. We also observed that long-term actively treated RA patients (n=55) exhibited a decreased endothelium-dependent vasodilatation (EDV) (mean±SD, 3.8+4.9%) compared with matched controls (8.0±4.5%).3

Sattar et al. also emphasized the importance of proinflammatory cytokines in the development of atherosclerosis in RA patients. Swiss investigators confirmed that tumor necrosis factor (TNF)–α blockade improved endothelial function in short-term–treated RA patients.4 We have recently assessed whether anti–TNF–α therapy was still effective in improving endothelial function in long-term anti–TNF–α–treated RA patients.5 We assessed this issue in 7 RA patients who had been treated with anti–TNF–α monoclonal antibody (infliximab) for at least 1 year and were receiving periodic treatment (every 8 weeks) with this drug.5 After infliximab infusion, we found a dramatic and rapid increase in the percentage of EDV.5 In all patients, values of percentage of EDV at day 2 after infusion (9.4±5.5%) were greater than those observed 2 days before infusion (2.8±2.5%). However, they returned to baseline by 4 weeks after drug infusion. This new observation highlights the importance of TNF–α in the mechanisms of atherosclerosis mediated by endothelial dysfunction in RA.

Finally, an important issue to be considered is the potential role of genetic factors in the development of atherosclerosis in RA patients. We assessed the influence of HLA-DRB1 status in the development of endothelial dysfunction in our series of 55 long-term actively treated RA patients.3 The percentage of EDV in all 7 HLA-DRB1*0404 patients was <3%. In contrast, only 22 of the 48 HLA-DRB1*0404–negative patients had a percentage of EDV <3%.3 These findings suggest that genetic factors may also be implicated in the development of atherosclerosis in RA.

The search for genetic markers associated with the development of atherosclerosis in RA and the use of drugs that may delay the progression of accelerated atherogenesis in RA constitute important issues to be addressed in the near future.

Carlos Gonzalez-Juanatey, MD
Miguel A. Gonzalez-Gay, MD, PhD
Cardiology Division
Rheumatology Division
Hospital Xeral-Calde
Lugo, Spain
miguelaggay@hotmail.com


Response

We thank Gonzalez-Juanatey and Gonzalez-Gay for their kind comments on our current perspective.1 The thrust of our article pointed toward the likely critical importance of chronic high-grade systemic inflammation for the accelerated atherogenesis in rheumatoid arthritis (RA). We are pleased to note their additional supportive data2 on the beneficial, albeit transient, effects of tumor necrosis factor–α monoclonal antibody (infliximab) on endothelium-dependent vasodilatation (EDV) in RA patients. It will be of interest to examine whether the changes in EDV correlated with changes in inflammatory factors in their study. Nevertheless, there is now a need for randomized studies to examine the extent to which other vascular risk factors (eg, insulin resistance, lipids, hemostatic factors, etc) known to be perturbed in RA can be improved by anti-inflammatory agents. Moreover, in the longer term, the potential vascular protective effects of statins in RA would be particularly important to establish in view of the apparent anti-inflammatory properties of this class of drugs.

Gonzalez-Juanatey and Gonzalez-Gay are correct to point out the importance of inflammation-related genetic factors in determining vascular risk in RA patients. Moreover, genetic risk likely lies not only in the HLA but also beyond in additional loci. For example, it is of interest that genetic polymorphism in the toll-like receptor 4 (TLR4) gene that is implicated in innate immunity is also associated with coronary atherosclerosis and predicts the risk of cardiovascular events.3,4 Complex interactions between environmental and genetic determinants in both the host immune system and the vasculature likely operate to modify vascular risk across the spectrum of inflammatory diseases.

Naveed Sattar, MD
David W. McCarey, MD
Hilary Capell, MD
Iain B. McInnes, MD
Department of Vascular Biochemistry and Centre for Rheumatic Diseases
North Glasgow Hospitals University NHS Trust
Glasgow Royal Infirmary
Glasgow, United Kingdom
nsattar@clinmed.gla.ac.uk
ibmi1w@clinmed.gla.ac.uk

Rheumatoid Arthritis and Accelerated Atherogenesis
Carlos Gonzalez-Juanatey and Miguel A. Gonzalez-Gay

Circulation. 2004;109:e328
doi: 10.1161/01.CIR.0000132731.43071.4F
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/25/e328

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/